PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
A61K 31/715, 7/48, 7/06

A1

(11) International Publication Number: **WO 93/16707**

(43) International Publication Date: 2 September 1993 (02.09.93)

(21) International Application Number: PCT/GB93/00343

(22) International Filing Date: 18 February 1993 (18.02.93)

(30) Priority data:
9203474.3 19 February 1992 (19.02.92) GB

(71) Applicant *(for all designated States except US):* SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : O'MULLANE, John, Edward [GB/GB]; SmithKline Beecham Consumer Brands, St George's Avenue, Weybridge, Surry KT13 0DE (GB). HAYTER, Ian, Peter [GB/GB]; SmithKline Beecham Consumer Brands, St George's Avenue, Weybridge, Surrey KT13 0DE (GB).

(74) Agent: WHITE, Susan, Mary; SmithKline Beecham, Corporate Patents, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB).

(81) Designated States: AU, CA, JP, NZ, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: LINSEED MUCILAGE

(57) Abstract

Compositions of matter comprising linseed mucilage and purified forms thereof having therapeutic and cosmetic utility for topical applications to the skin and/or mucous membranes of the body. Linseed mucilage compositions have mucoadherent properties; they may be used as an artificial mucus or lubricant and may be combined with active treating substances.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NL	Netherlands
BE	Belgium	GN	Guinea	NO	Norway
BF	Burkina Faso	GR	Greece	NZ	New Zealand
BG	Bulgaria	HU	Hungary	PL	Poland
BJ	Benin	IE	Ireland	PT	Portugal
BR	Brazil	IT	Italy	RO	Romania
CA	Canada	JP	Japan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo			SE	Sweden
CH	Switzerland	KR	Republic of Korea	SK	Slovak Republic
CI	Côte d'Ivoire	KZ	Kazakhstan	SN	Senegal
CM	Cameroon	LI	Liechtenstein	SU	Soviet Union
CS	Czechoslovakia	LK	Sri Lanka	TD	Chad
CZ	Czech Republic	LU	Luxembourg	TG	Togo
DE	Germany	MC	Monaco	UA	Ukraine
DK	Denmark	MG	Madagascar	US	United States of America
ES	Spain	ML	Mali	VN	Viet Nam
FI	Finland	MN	Mongolia		

LINSEED MUCILAGE

This invention relates to compositions of matter comprising linseed mucilage and purified forms thereof, processes for their preparation and cosmetic and therapeutic applications thereof.

Linseed mucilage is a viscous liquid obtained by an aqueous extraction of the seeds of the linseed plant. Linseed mucilage acts as a bulking agent and is used in the treatment of constipation. Linseed mucilage is recommended as a herbal remedy for the treatment of gastric disorders and for improving the general health of the digestive tract.

Various materials are known which adhere to the skin and/or mucous membranes of the body. An example of such a material is the complex of sulphated sucrose and aluminium hydroxide known as sucralfate. Compositions of these materials, referred to as bioadhesive materials have utility as muco-adherents and may be used by themselves or in conjunction with one or more therapeutically active materials.

It has now been found that linseed mucilage has bioadhesive properties which confer practical utility when the material is applied to the skin and mucous membrances of the body, both in isolation and in combination with other active treating substances. Tests have shown a positive mucus-mucilage interaction.

As a non-irritant, natural product, linseed mucilage has distinct advantages when applied to the body for cosmetic and/or therapeutic purposes.

According to the present invention, there is provided the use of a composition of matter comprising linseed mucilage for the manufacture of a medicament for topical application to the skin and/or mucous membranes of the human or animal body.

In another aspect, the invention provides the use of a composition of matter comprising linseed mucilage as a cosmetic preparation for topical application to the skin and/or mucous membranes of the human body.

Amongst the many and varied uses of linseed mucilage as a mucosal or mucous-adherent are included its use as an artificial mucus and/or lubricant for application to the skin surface, the occular, nasal, oral, vaginal and anal cavities; its use as a mucoadherent in the gastrointestinal tract; and its use as a cytoprotective agent.

Examples of the use of linseed mucilage as an artificial mucus and/or lubricant include its use in the treatment of dry-eye, xerostomia and radiotherapy induced secretory cell disorders, for example where the secretory cells in the salivary gland are destroyed.

As a cytoprotective agent, linseed mucilage has been shown to compare favourably with other muco-adherents, for example sucralfate, in preventing lesions.

It will be appreciated from the foregoing text that when used herein, the term topical application is not limited to application to the skin and/or exposed mucous surfaces of the body but rather includes any such surface, whether internal or external.

In addition, a composition of matter comprising linseed mucilage in combination with an active treating substance has utility as a delivery system for effecting localised and/or controlled release of the active treating substance. Such combinations, for example when administered orally, have moreover a cytoprotective effect and are useful in preventing or mitigating damage induced by said active treating substances.

Accordingly, the present invention provides a composition of matter comprising linseed mucilage in combination with an active treating substance. A method of controlled release treatment also constitutes an aspect of the invention.

When referred to herein, the term active treating substance includes medicaments, cosmetic substances and nutritional agents. Cosmetic substances as referred to herein include sun-screening agents, skin treatments such as skin softeners and anti-acne agents, perfumes and the like. Nutritional substances as referred to herein include vitamins and minerals. The term medicament as used herein refers to any therapeutic

substance, suitably any therapeutic substance that is effective via application to the skin or any of the mucous sites hereinbefore described.

Thus, combination of an active therapeutic substance with linseed mucilage can confer not only controlled release of the substance but, in addition, depending on the nature and purpose of the substance, retention of the substance at the target site promoting, *inter alia*, a localised effect at the target site, or, for substances which are absorbed either transdermally through the skin surface or via mucous surfaces, an effective means for delivering the active therapeutic substance to the systemic system.

An active treating substance as used in compositions of the present invention may be used singly or in combination with one or more other active treating substances.

An active treating substance, more particularly an active treating substance which is a medicament, will be present in the composition in an amount that is sufficient to prevent, cure and/or alleviate the condition requiring treatment. Such an amount is referred to hereinafter as an effective amount of the active treating substance.

The effective amount of a given active treating substance is dependent on the substance, for example its physico-chemical properties such as molecular weight and charge, the condition requiring treatment and the manner of administration. Such amounts may be determined by methods known in the art of biophysical chemistry.

Linseed mucilage for use in the present invention may be in the form of a viscous liquid, the viscosity of which may be selected to suit for example mode and/or site of administration. For example, for oral administration, liquid linseed mucilage preparations may be administered as a mouth rinse, wash or spray for retention in the oral cavity or as a liquid presentation, eg. a syrup for swallowing. Alternatively, linseed mucilage may be in a dried form for reconstitution with water prior to use, or for reconstitution on contact with body fluids at a mucous surface of the body. Linseed mucilage and purified forms thereof may for example be dried to form a powder or alternatively, cast as a thin film which on rehydration

adheres to the surface of the skin or mucuous membrane to which it is applied.

Linseed mucilage for use in the invention may be incorporated in a range of product presentations for oral delivery, including pastes and gelled products, such as gums, for example a chewing gum, and lozenge presentations. Presentations for oral delivery may be formulated for retention in the mouth, for example to be sucked, chewed or applied to the teeth or gums, or as presentations intended for swallowing. Where an active treating substance is combined with linseed mucilage and is intended to treat or prevent disorders associated with the oral cavity, the product is suitably formulated for retention in the mouth. Alternatively, where the active treating substance is intended to treat or prevent disorders requiring absorption of the substance from the gastrointestinal tract, the product may be formulated either for release of the active substance in the mouth or preferably a swallow product.

Processes for preparing raw linseed mucilage, dried forms thereof and gels, for example gum, lozenge and thin film formulations are a feature of the present invention.

Raw linseed mucilage may for example be obtained as a viscous, pseudoplastic liquid by boiling linseed in water, suitably for 2 to 10 minutes, favourably for 3 to 5 minutes, and filtering the product. Typically linseed mucilage having a dry weight of 1.0 to 1.6g per 100ml is obtained from an extraction of 1 part linseed to 10 parts water under these conditions. The seeds may be cracked prior to processing but use of whole, intact seed is generally preferred. Alternatively, linseed mucilage may be prepared from separated seed-coats. Percentage dry weight is dependent on a number of variables including for example seed-type and the extraction conditions employed for isolating the mucilage. Thus, linseed mucilage may also be obtained by aqueous extraction over a range of temperatures, for example at room temperature in which case the extraction process may extend over several hours. Mucilage obtained by extraction at or around room temperature generally has a lower percentage dry weight than material obtained by extraction at elevated temperature.

The liquid product may be dried using state of the art drying techniques, for example oven-, freeze- and spray-drying techniques, preferably an oven-drying or freeze-drying technique.

The native properties of the raw mucilage can be retained by combining it with gelling agents. Such agents would typically be gelatin, natural or synthetic gums. The gelation of the mucilage results in a retention of the native structure and the reconstitution upon dissolution of the gel matrix. The finished product may resemble dosage forms ranging from soft gels to hard lozenges.

It has also been found that the rheological properties, for example the pseudoplastic and bioadhesive properties of the raw mucilage are retained on rehydration of dried mucilage, more especially when the dried mucilage is prepared by oven-drying. During oven-drying the raw mucilage is suitably maintained at a temperature of about 60°C.

Purified forms of linseed mucilage also form part of the present invention. Dialysis of the mucilage against aqueous solutions removes low molecular weight materials that contribute to the odour and appearance of the mucilage. The dialysis of the mucilage against compositions of choice can be used in order to incorporate other components of formulations.

Raw mucilage may be subjected to ultrafiltration, to provide a high molecular weight mucilage fraction. Ultrafiltration, for example against a 10,000 molecular weight cut-off membrane against water, may be carried out prior to drying or gelling the raw linseed mucilage. Linseed mucilage which has been subjected to ultrafiltration retains the physical properties of raw mucilage. Morever, when raw mucilage is subjected to ultrafiltration prior to drying, the dried mucilage is obtained as a white, fibrous solid which retains the properties of the raw mucilage when rehydrated.

A further purified form a linseed mucilage is obtainable by treating raw linseed mucilage with a low molecular weight, water-soluble alcohol, for example a C_{1-6} alkyl alcohol, such as ethanol or isopropanol. Treatment with the alcohol causes precipitation of a component of the raw mucilage

which may be isolated as a fibrous solid.

The alcohol precipitated material has similar rheological characteristics to the raw mucilage when it is reconstituted into aqueous solutions. The precipitate and the reconstituted material lack the characteristic odour and colour of linseed mucilage. The reconstituted material is less subject to degradation than the raw material.

Alcohol precipitated linseed mucilage is accordingly a preferred form of mucilage according to the present invention.

The alcohol precipitated material, in common with raw mucilage, has been shown by chemical characterisation to consist of proteinaceous, saccharide and oil components in covalent or intimate admixture. A typical mucilage preparation may contain up to15% w/w of protein, up to 98% w/w of saccharides and up to 10% w/w of oils. The composition of a typical alcohol precipitated material is given in Example 4.

The present invention also provides linseed mucilage and a method of preparation thereof wherein the rheological properties, for example the viscosity of the mucilage in hydrated form, may be controlled to suit a chosen utility. It has for example been found that there is a marked difference in rheological behaviour between mucilage preparations, dependent on the amount of linseed used to prepare the raw mucilage. It has moreover been found that dilution of a concentrated or highly viscous mucilage preparation does not generate a homogenous mucilage preparation having reduced viscosity. The viscosity of such linseed mucilage preparations is rather controlled by varying the quantity of linseed present in the mixture of linseed and water during initial processing. The ability to reduce viscosity by dilution is a feature of mucilage preparations of low percentage dry weight which are formed initially as free-flowing viscous liquids. This supports the view that the rheology of linseed mucilage is at least partially determined by a concentration dependent polymeric entanglement.

The rheology of linseed mucilage preparations is also dependent on the linseed variety used to prepare the mucilage. It has been found for example that by subjecting a given amount of different seed types to

identical extraction processes, mucilages having a range of viscosities can be obtained.

It has also been found that rheology is dependent on the conditions under which the mucilage is extracted from the linseed. It has been shown that the viscosity of mucilage obtained by aqueous extraction is dependent on temperature, low temperature extraction generally giving rise to less viscous material than extraction at elevated temperature, for example by extraction with boiling water. Differences in rheology may be attributed, at least in part, to the molecular weight of the mucilage extract, extraction at elevated temperature giving rise to a higher proportion of high molecular weight materials.

By selection of seed-type, quantity of seed used and extraction conditions it is thus possible to obtain mucilages having viscosities in the range 5 to 5,000 cps and with a percentage dry weight in the range 0.1 to 3. Typically, a 1.2% dry weight mucilage will have an initial viscosity in the range 100 to 200cps.

The viscosity of linseed mucilage may therefore be selected to accommodate any one of the applications embodied in the present invention; the mucilage may range from a mobile liquid (eg. 5 to 50 cps, suitably 30 or 35 to 50cps), through a thick but nevertheless pourable liquid (eg. 50 to 300 cps, suitably 80 to 150cps) to a gellatinous composition (eg. greater than 300cps).

The ability to control the rheological properties of linseed mucilage renders it of utility as a viscosity controlling agent in liquid preparations, for example in liquid preparations for oral consumption. As a specific example linseed mucilage may be used as a sugar substitute in liquid syrups.

Accordingly, the use of linseed mucilage as a viscosity controlling agent forms an aspect of the present invention.

A yet further potential benefit of linseed mucilage for topical application to the human or animal body is derived from the effect of proteolytic enzymes on the rheological properties of the mucilage. It has been found

that the viscosity of a mucilage preparation is reduced as a function of time in the presence of proteolytic enzymes. It will be appreciated that proteolytic degradation can be used to advantage in applications according to the invention, for example when linseed mucilage is used as a drug delivery system. Particularly suitable applications include linseed mucilage incorporating an active treating substance for delivery to the occular, nasal or vaginal cavities of the body.

In addition to the optional presence of an active treating substance, compositions for use in the present invention may include pharmaceutically or cosmetically acceptable adjuvants for example excipients, lubricants, binders, gelling agents, preservatives, colouring agents and flavouring agents.

As stated above, linseed mucilage is a natural product already available for human consumption. Compositions according to the invention are substantially non-toxic to humans and animals, discounting any toxicity which may be associated with incorporation of an active treating substance. For the avoidance of doubt, the amount of active treating substance or effective amount of the active treating substance will be an amount that is not expected to confer any unacceptable toxicological effects.

Novel linseed mucilage formulations as hereinbefore described form part of the present invention as do their use as novel therapeutic agents, including their use in the treatment of gastric disorders.

Linseed mucilage preparations according to the present invention together with data illustrating their rheological properties are described in the following Examples. Linseed mucilage preparations according to the present invention may be prepared from any linseed variety.

Example 1

Preparation of Raw Linseed Mucilage

One part by weight linseed (seed type Hella) was added to ten parts by weight distilled water. The mixture was raised to boiling from room

temperature and boiled for four minutes. The hot extract was filtered under vaccum through a Buchner funnel with a pore size of approximately 1mm. The resulting mucilage was a viscous pseudoplastic liquid, pale golden in colour.

The mucilage was found to have a dry weight of 1.1 to 1.3g per 100ml. The material was stored at 4°C to avoid bacterial spoilage.

Example 2

Preparation of Dried Forms of Linseed Mucilage

a) Oven-Dried Mucilage

Raw linseed mucilage as prepared in Example 1 was placed on a flat stainless steel tray and dried in an oven at 60°C. The resulting yellow/brown film was ground and sieved.

b) Freeze-Dried Mucilage

Raw linseed mucilage as prepared in Example 1 was frozen in a conventional freezer. The frozen sample was subjected to freeze-drying in a freeze drier. The isolated, freeze-dried mucilage was a fibrous, low-density pale yellow powder.

Example 3

Preparation of Ultrafiltered Linseed Mucilage

Raw linseed mucilage as prepared in Example 1 was subjected to ultrafiltration through a 10,000 molecular weight cutoff membrane against water. This process removed the colouration and most of the odour of the raw mucilage, but retained its pseudoplastic properties. The ultrafiltrated mucilage was then freeze-dried to give a dried linseed mucilage as a white fibrous material.

Example 4

Preparation of Isopropanol Precipitated Linseed Mucilage

Raw linseed mucilage as prepared in Example 1 was treated with an equal volume of isopropyl alcohol. This treatment precipitated out approximately 80% of the dry weight of the mucilage comprising the protein, saccharide and some residual oil component of the raw mucilage. The initial precipitate was a white, odourless, fibrous material which rehydrated to a mucilage-like material on exposure to air.A typical mucilage preparation would have the following characteristics:

a)

	% dry w/w
Protein	0 - 10
Saccharide	10 - 98
Oil	0 - 10
Mineral	0 - 20

Such components may exist as admixtures, intimate mixes or covalent structures such as a glycoprotein or glycolipid.

b) Sugar type

	% w/w
Galacturonic	0 - 20
Galactose	20 - 45
Arabinose	10 - 40
Xylose	10 - 45
Rhamanose	0 - 20

c) Amino acid composition

	% (w/w)
Acidic	20-60
Basic	5-20
Sulphur-containing	0-10
Aliphatic	5-20
Aromatic	0-15
Neutral	10-50

d) Nitrogen Content (Kjeldahl det^{n})

% Nitrogen = 0.89 (dry weight basis)
Nitrogen conversion factor = 5.88 (calculated from amino acid data)
Peptide/protein content = 5.23%

e) Viscosity (Brookfield Viscometer)

Viscosity may range from: 5 to 5000 cps

f) Action of Proteolytic Enzyme

The viscosity of a 1% solution fell from 130 cp to 30 cp on standing overnight at room temperature.

g) Gel Electrophoresis

No low molecular weight peptide/protein was detected. The material behaved as a single compound of very high molecular weight.

Example 5

Rheology Studies

Rheology studies were carried out on raw linseed mucilage as prepared in Example 1 using a Carri-Med controlled stress rheometer and an oscillatory Carri-Med rheometer.

Studies with the Carri-Med controlled stress rheometer were carried out using a stainless steel cone and plate.

Operating Conditions: 4 cm 2° cone 70μm gap at 25°C.

Studies with the oscillatory Carri-Med rheometer were carried out maintaining the force applied to less than 1% of the force where destruction of the mucilage had been observed.

The flow curves obtained from both studies indicate that raw linseed mucilage is pseudoplastic and that shear thinning is destructive. The 1% raw mucilage had the properties of a weak thixotropic pseudoplastic gel. The gel structure has been shown to be concentration dependent. Linseed mucilages of lower concentration than that of Example 1 were prepared by boiling together varying masses of seed and water. Mucilage preparations, less concentrated than that obtained in Example 1, were prepared by using less seed in the extraction proccess rather than by dilution of the concentrated preparation. A marked difference between the rheological behaviour of the different concentration mucilage preparations was observed. It was observed that linseed mucilage of less than 1% dry weight rapidly lost pseudoplastic/thixotropic gel properties as concentration decreased, suggesting that gel rheology is partially dependent upon a concentration dependent polymeric entanglement.

Example 6

Rehydration analysis

A visual assessment of the rehydration of the various dried materials was conducted. known quantity of the test material (approx. 100mg.) was mixed with 10ml. of distilled water or 0.1M Hydrochloric acid. The suspensions/solutions were monitored for several days whilst being mixed by gentle inversion. The results were as follows:

Oven dried Mucilage - this gave a mucilage like material, with reduced pseudoplastic properties. The resuspension time was the shortest of any

of the materials tested. Resuspension in hot/boiling water produced similar results. Coarse powders resuspended more readily than fine powders. In 0.1M Hydrochloric acid there appeared to be some evidence that the material was less viscous than when rehydrated in water.

Freeze dried Mucilage - freeze dried powders proved difficult to wet, the material attaining a 'swollen volume' with time. The time taken to reach this final swollen volume was measureable in days. Hot and boiling water produced very similar results. The material rehydrated in acid appeared slightly less viscous.

Spray dried Mucilage - The rehydration of the material was examined in both water and 0.1M hydrochloric acid. The spray dried material formed a swollen mass in both environments, this slowly dispersed over several days to form a dark brown liquid/suspension. The material in 0.1M acid appeared to be slightly less viscous than that in water. The addition of boiling water to the spray dried mucilage appeared to have no effect upon the rehydration.

Freeze dried ultrafiltrated Mucilage - this material appeared to behave in a manner identical to that seen in the freeze dried material. There was some evidence that the pseudoplasticity of the material had been reduced by the shear forces generated by the stirring within the untrafiltration cell.

The resuspensions were graded as follows in order of appearance compared to raw mucilage:

Oven dried > Freeze dried > Spray dried.

Example 7

Mucoadhesion Assay

A comparison of the mucoadhesion of the dried forms of linseed mucilage was made using a method based upon a tensiometer study of adherence to porcine gastric mucous. The adhesive properties of raw linseed mucilage were also compared to those shown by porcine stomach mucous. The dried

mucilage and the raw mucilage experiments included a negative control (Acacia) and a positive control (polyacrylic acid, PAA).

Materials

Acacia BP
Polyacrylic acid (PAA)
Spray-dried Linseed Mucilage (SDLM)
Oven-dried (60°C) Linseed Mucilage (ODLM)
Freeze-dried Linseed Mucilage (FDLM)
Raw Linseed Mucilage (~1.52% w/w).

Apparatus

Torsion Balance (5g; full scale White Electrical Instrument Co Ltd).
Rubber supports (BDH Ltd)

Experimental Procedure

Assessment of mucoadhesion using a surface tensiometer

The adhesion of potential mucoadhesive materials to mucous was assessed using a surface tensiometer. Powdered polymer was spread on rubber discs (8mm diameter) which had been coated previously with an adhesive resin. A disc was then mounted on a glass rod which had been coated previously with an adhesive resin. A disc was then mounted on a glass rod which in turn was supended from a 5g tension balance. The diluted mucous (15ml) was transferred to a jacketed beaker cooled to 22°C and raised slowly until contact with the coated disc was made. After contact times of 0, 2, 5 and 10 mins the disc was raised at a rate corresponding to 50mg s^{-1} until detachment occurred. Control experiments were carried out in an identical manner, using adhesive resin-coated discs without polymer immediately after each material was tested. The weight required for detachment was recorded in each case (n=3-4).

The optimum equilibration time for Polyacrylic Acid (PAA) and Acacia coated discs obtained using mucous were used in similar experiments in which the mucous was substituted with freshly prepared linseed

mucilage. The weight required to detach each material from the mucous was expressed as a percentage of the weight required to detach the control disc from the mucous.

Results

Table 1 shows the results obtained for the detachment weights of the investigative materials from mucous, expressed as a percentage of the control.

Table 1: Detachment weight of various investigative polymeric extracts from mucous (expressed as a percentage of the control)

Contact Time (min)	PAA	ODLM	SDLM	FDLM	Acacia
0	117.9	157.8	108.9	119.0	91.30
	126.3	120.4	106.1	113.6	87.23
	128.9	139.1	110.9	120.9	91.11
mean	124.4	139.0	108.6	117.8	89.9
10	144.6	141.1	124.5	118.1	94.4
	147.3	136.8	120.8	132.0	98.2
	156.1	137.5	132.7	120.0	96.3
mean	149.3	138.5	125.9	123.3	96.3

Table 2 shows the corresponding detachment values which were obtained when polyacrylic acid (PAA) and acacia were detached from raw linseed mucilage in place of mucous.

Table 2: Mean Detachment weight (expressed as a percentage of the control) of Polyacrylic acid (PAA) and acacia from freshly constituted linseed mucilage, employing a contact time between polymer and mucilage of 5 minutes

Polymer	Mean Detachment weights % (± SEM)
PAA	159.3 (14.55)
Acacia	131.4 (6.62)

For all of the linseed mucilage extracts and PAA, when the coated rubber support was disengaged from the mucous, the origin of detachment was clearly from within the mucous layer, a portion of mucous always remaining adhering to the polymer after detachment had occurred. For the control supports, coated only with adhesive resin, the origin of detachment was clearly at the mucous interface, no mucous being associated with the rubber support. Detachment usually also occurred at the mucous/air interface when Acacia was employed as the coating polymer. Acacia exhibited signs of some dissolution in the mucous gel and this may partially account for the lack of mucoadhesive potential.

When mucous was substituted with linseed mucilage, empolying a 5 min contact time, marked differences between the detachment weights of PAA and Acacia were also found. The mean detachment from the mucilage for PAA of 159.3% compared favourably with its mean detachment from mucous (154.6%) whereas the detachment value of Acacia from the mucilage (132.7%) was markedly higher than the corresponding value from the mucous gel (103.0%). Two features of the mucilage-detachment experiments are worthy of comment. First, it was noted that the pattern of separation of the PAA from the mucilage was different to that of the Acacia and different also to the pattern of separation of PAA from mucous. In the case of PAA-mucilage detachment the linseed mucilage was pulled into long threads and in some cases separation was not achieved at all.

Example 8

Gelation of Raw Linseed Mucilage

Raw linseed mucilage as prepared in Example 1 was gelled by addition of the following external gelling agents:

1% Gellan gum
0.5% Gellan gum
7% Gelatine

The resulting gels retained their mucilage like properties when diluted using hot water.

Example 9

Gelation of Isopropanol Precipitated Linseed Mucilage

Isopropanol precipitated linseed mucilage as prepared in Example 4 was suspended in water and treated with gelling agents as described in Example 8. The resulting gels, on treatment with hot water, rehydrated to provide a colourless, odourless mucilage.

Example 10

Cytotoxicity Assay

Method

In a standard ethanol-induced gastritis model, the raw mucilage, and more effectively the precipitated material, has been shown to reduce lesion formation. The test articles were pre-dosed.

Results

Test Article	Lesion score
Water	50.9
1% water reconstituted precipitate	42.5
2% water reconstituted precipitate	20.3
2% Polycarbophil	28.1
2% Sucralfate	21.1

Example 11

Linseed Mucilage Drug Complexes

Preparation

Drug-mucilage complexes were prepared from linseed mucilage and each of the following compounds: dyclonine, phenylephrine, lignocaine, cimetidine, loperamide, cetyl pyridinium choride (CPC) and chlorhexidine. The complexes were prepared by adding a known quantity of an aqueous solution of the drug to a known volume of linseed mucilage prepared as

per Example 1. On mixing mucilage with CPC and chlorhexidine, the complex formed as a flocculant precipitate which was separated from the aqueous supernatant by centrifugation, washed with water and filtered. The drug content of these two complexes was determined by HPLC analysis of dried samples.

Drug Release from Complexes

For drugs that did not form a precipitate with mucilage, the rate of drug release was measured by dialysis of a 1:1 mixture of complex and an aqueous solution of the drug. All experiments were carried out using water as the release medium. An aqueous solution containing the same amount of drug as in the mucilage solutions was simultaneously dialysed with water to act as control.

For CPC and chlorhexidine which formed a precipitate, known amounts of precipitate were dialysed relative to aqeous controls containing the same amount of drug as found in the precipitate (by HPLC). Control dialyses were simultaneously carried out in water.

A series of samples were taken for analysis over a period of four hours for all drugs tested. Drugs showing incomplete release after this time were examined over a longer period. The results shown are means from duplicate HPLC injections.

Results

Dialysis of Cetyl Pyridinium Choride (125mg as CPC/5g into 500ml)

CPC Released (mg/100ml)

Time	Control	Precipitate
1	0.06	0.03
5	0.01	0.01
10	0.04	0.03
15	0.04	0.04
30	0.17	0.11
45	0.28	0.20
60	0.39	0.29
90	0.70	0.48
120	0.96	0.66
180	1.65	1.04

Time	Control	Precipitate
240	2.40	1.42
300	3.16	1.86
360	3.96	2.18
420	4.70	2.58
1440	14.36	6.23
1800	16.62	6.79

Dialysis of Chlorhexidine/Mucilage Precipitate

(80mg as chlorhexidine gluconate/5g into 500ml)

Chlorhexidine Gluconate Released (mg/100ml)

Time	Control	Precipitate
1	0.27	0.04
5	0.80	0.10
10	1.37	0.18
15	1.94	0.25
30	3.50	0.43
45	4.96	0.60
63	6.51	0.79
90	8.39	1.00
120	10.10	1.23
180	12.52	1.59
240	13.75	1.90
300	14.63	2.15
360	15.26	2.37
4200	16.72	4.88

Dialysis of Lignocaine HCl (20.2mg/5ml into 500ml)

Lignocaine HCl Released (mg/100ml)

Time	Control	50% Mucilage
1	0.16	0.11
5	0.56	0.37
10	0.94	0.61
15	1.30	0.80
30	2.11	1.25
45	2.66	1.54
60	3.01	1.90
90	3.45	2.34
120	3.66	2.64
180	3.79	3.05
240	3.90	3.25
300	3.92	3.31
1185	3.94	3.73

Dialysis of Phenylephrine HCl

(27.5mg/5ml into 500ml)

Phenylephrine HCl Released (mg/100ml)

Time	Control	50% Mucilage
1	0.19	0.17
5	0.70	0.55
10	1.29	0.95
15	1.82	1.26
30	3.04	2.10
45	3.83	2.76
60	4.18	3.26
90	5.00	3.88
120	5.32	4.24
180	5.40	4.48
240	5.39	4.84
1440	5.69	5.40

Dialysis of Loperamide HCl

(16.5mg/5ml into 500ml)

Loperamide HCl Released (mg/100ml)

Time	Control	50% Mucilage
1	0.07	0.04
5	0.24	0.12
10	0.44	0.22
15	0.64	0.32
30	1.14	0.56
45	1.59	0.79
58	1.88	0.98
90	2.35	1.32
120	2.61	1.61
180	2.90	2.01
240	3.09	2.26
1200	3.32	3.03

Dialysis of Dyclonine HCl

(20.2mg/5ml into 500ml)

Dyclonine HCl Released (mg/100ml)

Time	Control	50% Mucilage
1	0.16	0.08
5	0.34	0.30
10	0.87	0.49
15	1.17	0.65
30	1.89	1.04
45	2.44	1.36
60	2.84	1.59
90	3.40	1.98
120	3.68	2.27
180	4.00	2.70
240	3.94	2.91
300	3.99	3.19
360	4.07	3.37
1260	4.06	4.00

Dialysis of Cimetidine

(17.5mg/5ml into 500ml)

Cimetidine Released (mg/100ml)

Time	Control	50% Mucilage
1	0.10	0.10
5	0.32	0.33
10	0.50	0.54
15	0.68	0.71
30	1.16	1.12
45	1.58	1.40
60	1.92	1.67
90	2.46	2.05
120	2.85	2.30
180	3.35	2.71
240	3.55	3.00

(50% Mucilage = 1:1 dilution of mucilage)

Claims

1. The use of a composition of matter comprising linseed mucilage or a purified form thereof for the manufacture of a medicament for topical application to the skin and/or mucous membranes of the human or animal body.

2. The use of a composition of matter comprising linseed mucilage or a purified form thereof as a cosmetic preparation for topical application to the skin and/or mucous membranes of the human body.

3. Use as claimed in claim 1 or claim 2 characterised in that the composition is applied to the skin surface, or the occular, nasal, oral, vaginal or anal cavities.

4. Use as claimed in claim 1 or claim 2 characterised in that the linseed mucilage is obtainable by aqueous extraction at elevated temperature.

5. Use as claimed in claim 1 or claim 2 characterised in that the linseed mucilage is obtainable by alcohol precipitation.

6. Use as claimed in claim 1 or claim 2 characterised in that the linseed mucilage is purified by dialysis.

7. Use as claimed in claim 1 or claim 2 characterised in that the linseed mucilage is purified by ultrafiltration.

8. Use as claimed in claim 1 or claim 2 characterised in that the linseed mucilage has a molecular weight above 10,000.

9. Use as claimed in claim 1 or claim 2 characterised in that the linseed mucilage has a percentage dry weight in the range 0.1 to 3.0.

10. Use as claimed in any one of claims 1 to 9 characterised in that the composition is applied to the skin surface, or the occular, nasal, oral, vaginal or anal cavities as an artificial mucus and/or lubricant.

11. Use as claimed in any one of claims 3 to 9 characterised in that the composition is administered orally and functions as a mucoadherent in the gastrointestinal tract.

12. Use as claimed in any one of claims 3 to 9 characterised in that the composition is administered orally and functions as a cytoprotective agent.

13. Linseed mucilage in purified form obtainable by alcohol precipitation.

14. A composition of matter comprising linseed mucilage or a purified form thereof in combination with an active treating substance.

15. A composition of matter comprising linseed mucilage or a purified form thereof, optionally in combination with an active treating substance, in the form of a powder, a paste, a gum, a lozenge or a thin film.

16. Purified linseed mucilage as claimed in claim 13 or a composition as claimed in claim 14 or claim 15 for use in therapy.

17. Use of purified linseed mucilage or a composition as claimed in claim 14 or claim 15 as a cosmetic preparation.

18. Use of linseed mucilage as a viscosity controlling agent.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 93/00343

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K31/715; A61K7/48; A61K7/06

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	GETREIDE, MEHL UND BROT vol. 26, no. 4, 1972, page 99 D.WEIPERT 'Über die Schleimstoffe des Leinsamens' see the whole document ---	1-18
X	MATER. MED. POL. (ENGL.ED.) vol. 9, no. 1, 1977, pages 46 - 48 Z.OLSZEWSKI ET AL. 'Studies on the original method...' see page 48 --- -/--	1-18

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
24 JUNE 1993	08.07.93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	THEUNS H.G.

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	ACTA AGRIC. SCAND. vol. 41, no. 3, 1991, pages 311 - 320 K.WANNENBERGER ET AL. 'Rheological and Chemical Properties of Mucilage in Different Varieties from Linseed (Linum usitatissimum)' see page 311	1-18
X	RES. IND. (NEW DEHLI, INDIA) vol. 15, no. 2, 1970, pages 91 - 94 (MISS) B.M. TRIVEDI ET AL. 'Linseed Mucilage as a Substitute for the Commonly Used Suspending Agents' see the whole document	1-18
X	INDIAN J. PHARM. SCI. vol. 50, no. 2, 1988, pages 89-92 - 97 S.K.BAVEJA ET AL. 'Examination of Natural Gums and Mucilages as Sustaining Materials in Tablet Dosage Forms' see the whole document	1-18
X	J.FOOD SCI. TECHNOL. vol. 26, no. 1, 1989, pages 16 - 20 N.S.SUSHEELAMMA 'Functional Role of Linseed (Linum usitatissimum L.) Polysaccharide in Steamed Pudding (idli)' see the whole document	1-18
X	FARM. POL. vol. 39, no. 5, 1983, pages 271 - 274 L. WENDT ET AL. 'Próby Zastosowania slusów....' see abstract	1-18
X	PHARM. IND. vol. 37, no. 10, 1975, pages 836 - 839 E.MINKOW ET AL. 'Some Biopharmaceutical Studies....' see the whole document	1-18

-/--

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	J. FOOD TECHNOL. vol. 24, no. 3, 1987, pages 103 - 106 N.S.SUSHEELAMMA 'Isolation and Properties of Linseed Mucilage' see page 103, left column	1-18
X	US,A,3 338 304 (J.L.LUMMUS) 29 August 1967 see the whole document	1-18
X	FARM. POL. vol. 41, no. 10, 1985, pages 580 - 583 M.SUSKA ET AL. 'Badanie wlasciwosci...' see abstract	1-18
X	CHEMICAL ABSTRACTS, vol. 83, 1975, Columbus, Ohio, US; abstract no. 136845a, J.POREBSKI 'Tablets with prolonged action...' see abstract & ACTA POL. PHARM. vol. 32, no. 1, 1975, pages 121 - 123	1-15
X	CHEMICAL ABSTRACTS, vol. 98, 1983, Columbus, Ohio, US; abstract no. 59931f, 'Mucilage for use in pharmaceuticals' see abstract & RO,A,65 883 (D.C.CRACIUN) 30 April 1989	1-18
X	CHEMICAL ABSTRACTS, vol. 102, 1985, Columbus, Ohio, US; abstract no. 97263y, 'Natural hydrocolloids from linseed,...' see abstract & PL,A,122 225 (M.JOSZWIAK) 3 August 1979	1-18
X	CHEMICAL ABSTRACTS, vol. 103, 1985, Columbus, Ohio, US; abstract no. 27089t, 'Cosmetics with moisturizing action' see abstract & RO,A,83 316 (L.GEORGESCU) 28 February 1984	1-18

-/--

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9300343
SA 70975

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 24/06/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-3338304		None	
BE-A-468600		None	
FR-A-2157676	08-06-73	None	
FR-A-899129		None	
FR-M-3848		None	

EPO FORM P0479

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82